The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial

Else Charlotte Sandset, Philip M W Bath, Gudrun Boysen, Dalius Jatuzis, Janika Kõrv, Stephan Lüders, Gordon D Murray, Przemyslaw S Richter, Risto Ö Roine, Andreas Terént, Vincent Thijs, Eivind Berge, on behalf of the SCAST Study Group

Summary

Background Raised blood pressure is common in acute stroke, and is associated with an increased risk of poor outcomes. We aimed to examine whether careful blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan is beneficial in patients with acute stroke and raised blood pressure.

Methods Participants in this randomised, placebo-controlled, double-blind trial were recruited from 146 centres in nine north European countries. Patients older than 18 years with acute stroke (ischaemic or haemorrhagic) and systolic blood pressure of 140 mm Hg or higher were included within 30 h of symptom onset. Patients were randomly allocated to candesartan or placebo (1:1) for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on days 3 to 7. Randomisation was stratified by centre, with blocks of six packs of candesartan or placebo. Patients and investigators were masked to treatment allocation. There were two co-primary effect variables: the composite endpoint of vascular death, myocardial infarction, or stroke during the first 6 months; and functional outcome at 6 months, as measured by the modified Rankin Scale. Analyses were by intention to treat. The study is registered, number NCT00120003 (ClinicalTrials.gov), and ISRCTN13643354.

Findings 2029 patients were randomly allocated to treatment groups (1017 candesartan, 1012 placebo), and data for status at 6 months were available for 2004 patients (99%; 1000 candesartan, 1004 placebo). During the 7-day treatment period, blood pressures were significantly lower in patients allocated candesartan than in those on placebo (mean 147/82 mm Hg [SD 23/14] in the candesartan group on day 7 vs 152/84 mm Hg [22/14] in the placebo group; p=0.0001). During 6 months’ follow-up, the risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events; placebo, 111 events; adjusted hazard ratio 1.09, 95% CI 0.84–1.41; p=0.52). Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group (adjusted common odds ratio 1.17, 95% CI 1.00–1.38; p=0.048 [not significant at p≤0.025 level]). The observed effects were similar for all prespecified secondary endpoints (including death from any cause, vascular death, ischaemic stroke, haemorrhagic stroke, myocardial infarction, stroke progression, symptomatic hypotension, and renal failure) and outcomes (Scandinavian Stroke Scale score at 7 days and Barthel index at 6 months), and there was no evidence of a differential effect in any of the prespecified subgroups. During follow-up, nine (1%) patients on candesartan and five (<1%) on placebo had symptomatic hypotension, and renal failure was reported for 18 (2%) patients taking candesartan and 13 (1%) allocated placebo.

Interpretation There was no indication that careful blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan is beneficial in patients with acute stroke and raised blood pressure. If anything, the evidence suggested a harmful effect.

Introduction Raised blood pressure is common in patients with acute stroke, and is associated with poor short-term and long-term outcomes. The hypertensive response can have several causes, including inadequately treated or undiagnosed hypertension, stress response with activation of neuroendocrine systems, damage to autonomic centres in the brain, and increased intracranial pressure.

The optimum management of blood pressure in acute stroke is not known, and current practice is to accept high blood pressure in this situation. Under normal circumstances, cerebral autoregulation sustains constant cerebral blood flow across an extensive range of systemic blood pressures. In acute stroke, the autoregulatory mechanism can be impaired or damaged, and cerebral tissue perfusion relies on systemic blood pressure. In this situation, blood-pressure reduction can compromise perfusion of the penumbra and cause further infarction, as suggested by a small trial of intravenous nimodipine. Conversely, high blood pressure can cause brain oedema or haemorrhage, and data from the International Stroke Trial showed a clear association between systolic blood...
pressure in the acute phase and early death and poor long-term outcome.

The angiotensin-receptor blocker candesartan has shown promising effects on infarct size and neurological status in several experimental studies.\(^\text{11,12}\) The ACCESS study\(^\text{13}\) of 342 patients with acute stroke and high blood pressure suggested that treatment with candesartan during the first week of stroke reduces the incidence of vascular events and deaths during the first 12 months (odds ratio [OR] 0·48, 95% CI 0·25–0·90). The mechanisms by which angiotensin-receptor blockers can affect the risk of death and vascular events are unknown. Studies of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers in cardiovascular disease suggest specific neuroprotective effects beyond the effects of blood-pressure lowering,\(^\text{14–16}\) but whether similar effects can be seen in acute stroke remains to be shown. We aimed to assess whether careful blood-pressure lowering treatment with candesartan is beneficial in a wide range of patients with acute stroke and raised blood pressure.

**Methods**

**Study design and participants**

The Scandinavian Candesartan Acute Stroke Trial (SCAST) was a north European, multicentre, randomised, placebo-controlled, double-blind trial of candesartan in patients with acute stroke and raised blood pressure. Details of the design have been reported elsewhere.\(^\text{\textsuperscript{17}}\) Patients aged 18 years or older with a clinical diagnosis of stroke (ischaemic or haemorrhagic), presenting within 30 h of symptom onset and with systolic blood pressure higher than 140 mm Hg were potential candidates for inclusion. Exclusion criteria were contraindications to or current treatment with an angiotensin-receptor blocker, markedly reduced consciousness (Scandinavian Stroke Scale [SSS] consciousness score ≤2),\(^\text{18}\) clear indication, in the clinician’s view, for an angiotensin-receptor blocker during the treatment period (eg, patients with chronic heart failure and intolerance to ACE inhibitors), clear indication for antihypertensive treatment during the acute phase of stroke, known premorbid modified Rankin Scale (mRS) score of 4 or more,\(^\text{19}\) life expectancy of 12 months or less, patient unavailability for follow-up, and pregnancy or breastfeeding.

Written informed consent was sought from all patients. Non-written or waiver of consent was accepted only after approval from the ethics committees. The trial complied with Good Clinical Practice standards and with the Declaration of Helsinki.\(^\text{20}\) The study is registered, number NCT00120003 (ClinicalTrials.gov), and ISRCTN13643354. The EudraCT number is 2004-002187-22.

**Randomisation and masking**

Patients were allocated in a 1:1 ratio to treatment with candesartan or placebo. The randomisation sequence was computer-generated and stratified by centre, with blocks of six packs of candesartan or placebo. Patients and investigators were masked to treatment allocation; the candesartan and placebo tablets were identical in appearance and came in prepacked, consecutively numbered drug packs. Randomisation was done centrally via a secure website. Each patient was assigned a randomisation number and received tablets from the corresponding drug pack. If internet access was not available, investigators could use the drug pack with the lowest number.

**Procedures**

Demographic and clinical characteristics were recorded before randomisation. Blood pressure was measured twice with an interval of 10 min with a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA). The first dose of trial treatment was administered within an hour of the last reading. There was a fixed-dose escalation scheme: 4 mg on day 1, 8 mg on day 2, and 16 mg on days 3–7. Patient compliance was assessed by daily recordings of the doses that the patients received. Blood pressure was measured daily during the morning round with the patient in the supine position, after 5 min of rest, using the automated monitor provided and the same arm that was used at randomisation. Dose adjustments were made if systolic blood pressure was lower than 120 mm Hg or when clinically indicated. All patients received standard treatment in stroke units, and therapeutic agents other than angiotensin-receptor blockers could be administered
at the local investigators’ discretion, including additional antihypertensive drugs in case of severe and sustained hypertension.

Clinical visits took place on day 7 and at 1 and 6 months. At 3 months, the trial coordinating centre did a telephone or postal interview. To avoid important differences in treatment during follow-up, candesartan was the advised antihypertensive treatment and was provided free of charge. All treatment during follow-up, including treatment with candesartan, was left to the discretion of the investigators.

There were two co-primary effect variables: the composite endpoint of vascular death, non-fatal myocardial infarction, or non-fatal stroke during the first 6 months; and functional status at 6 months, as measured by mRS. Secondary effect variables were death from all causes, vascular death, ischaemic stroke, haemorrhagic stroke, all stroke, myocardial infarction, stroke progression, neurological status at 7 days (as measured by the SSS), and activities of daily living (as measured by the Barthel index\textsuperscript{21}). Safety variables were symptomatic hypotension and renal failure. Stroke progression was defined as a neurological deterioration of 2 or more points on the SSS occurring within the first 72 h of stroke onset and believed to be caused by the index stroke, after exclusion of recurrent stroke or systemic reasons for deterioration. The SSS has a range of 0 (maximum neurological deficits) to 58 (no deficits), and the SSS and the definitions of other serious adverse events are shown in webappendix pp 1–2. All serious adverse events reported by the investigators were adjudicated by a masked, independent event adjudication committee.

Data quality was monitored centrally. Additionally, a random sample of 10% of all centres was visited for local monitoring. The independent data monitoring committee reviewed the overall quality of the trial and undertook an unmasked interim analysis when half of the patients had been included, in accordance with the protocol.

Statistical analysis

On the basis of previous trials, we expected that 18% of the patients in the placebo group would have reached the composite vascular endpoint and that 60% would be dead or disabled at 6 months. We estimated that 2200 patients would be needed to detect an absolute risk reduction of 6% in death or major disability (using a conventional fixed dichotomy analysis) or a relative risk reduction of 25% for the composite vascular endpoint, with 80% statistical power and a 5% significance level. Target recruitment was set at 2500 patients, to account for the
Analyses were done according to a detailed, prespecified statistical analysis plan (webappendix pp 3–7). For analysis of the composite vascular endpoint, we used the Cox proportional hazards regression model; for functional outcome, we used ordinal logistic regression. Both analyses were adjusted for age, cause of stroke (ischaemic vs all other), systolic blood pressure, and SSS score at baseline. Although the sample size calculation was based on a conventional fixed dichotomy of functional outcome, the protocol specified that an ordinal method should be used for analysis. The choice of ordinal logistic regression was based on the results of statistical research, which showed that ordinal methods could increase statistical power substantially, equivalent to allowing a reduction of the order of 30% in the sample size without loss of statistical power. Ordinal regression is based on the assumption that the odds ratio is the same at each cutpoint on the mRS, an assumption that can be tested with a formal test of goodness of fit. The sliding dichotomy method and the conventional fixed dichotomy method were done as sensitivity analyses.

The Hochberg method was applied to allow for the two co-primary effect variables, so that a p value of 0·025 or less had to be achieved with one of the primary effect variables, or a p value of 0·05 or less had to be achieved with both primary effect variables, before a treatment effect could be claimed significant at the 5% significance level. This approach is conservative, since death is included in both co-primary effect variables—ie, they are not independent. The secondary effect variables were analysed with parametric methods if appropriate and non-parametric methods otherwise. Prespecified subgroup analyses were done with the co-primary effect variables (webappendix pp 3–7).

All patients randomly assigned to treatment groups were included in the intention-to-treat analysis, and a per-protocol analysis was done on all patients treated in accordance with the protocol. For patients who were alive at 6 months, but who had not been given an mRS score, we carried forward the mRS score from the last
hospital visit at 1 month. We used SPSS (version 18.0) for all analyses.

Role of the funding source
The trial coordinating centre, with assistance from the independent trial steering committee, was responsible for the conduct of the trial. The trial was funded by grants from the South-Eastern Norway Regional Health Authority and Oslo University Hospital Ullevål. AstraZeneca supplied the study drugs, and AstraZeneca and Takeda supported the trial with limited, unrestricted grants. AstraZeneca and Takeda’s representatives in the trial steering committee were non-voting and had no role in data collection or analysis, the writing of the report, or the decision to submit for publication.

Results
2029 patients were recruited from 146 centres in Belgium, Denmark, Estonia, Finland, Germany, Lithuania, Norway, Poland, and Sweden between June 5, 2005, and Feb 25, 2010 (figure 1). Patient recruitment was stopped before the intended sample size was reached because recruitment was slower than had been expected and the research grant expired. The decision to stop patient recruitment was made in May, 2009, by the trial steering committee. It was based purely on administrative grounds, without knowledge of the data.

During the trial, screening logs of all patients admitted with a suspected stroke were recorded at 14 centres, which contributed 17% of all patients. The main reasons for exclusion were: symptom duration of 30 h or longer (708 patients, 34%), systolic blood pressure lower than 140 mm Hg (521, 25%), SSS consciousness score of 2 or lower (289, 14%), no limb affection (256, 12%), ongoing treatment with an angiotensin-receptor blocker (124, 6%), other serious disease (105, 6%), unwillingness to participate (69, 3%), transient ischaemic attack (TIA; 43, 2%), and other causes (133, 6%). Of the 2029 patients included in the trial, four patients were lost to follow-up and 21 withdrew consent, but data for status at 6 months were available for the remaining 2024 patients (99%). For four patients who were alive at 6 months, but who had not been given an mRS score (two in each group), we carried forward the mRS score from the last hospital visit at 1 month.

Table 1 shows the baseline characteristics of the included patients. Demographic and clinical characteristics were well balanced between treatment groups, except that there were more patients with a history of previous stroke or TIA and fewer women in the candesartan group than in the placebo group. The mean age was 71 years, mean symptom duration before randomisation was 18 h, mean SSS score was 41 (equivalent to a US National Institutes of Health Stroke Scale score of 8°), and mean blood pressure was 171/90 mm Hg. 1733 patients (85%) had ischaemic stroke, 274 (14%) had haemorrhagic stroke, and 20 (1%) did not have a stroke (of whom 13 had TIA).

Compliance with the trial treatment was good throughout the treatment period. The mean proportion of patients receiving study drugs was 97% in both groups (965 patients allocated candesartan, 971 placebo), and of patients taking study drugs, 908 (94%) in the candesartan group and 923 (95%) in the placebo group received the dose recommended in the protocol. Treatment with other antihypertensive agents was given equally in the two groups, including ACE inhibitors (candesartan, 275 patients, 28%; placebo, 262 patients, 26%). Slightly fewer patients in the candesartan group than in the placebo group used candesartan during follow-up (688 candesartan patients and 730 placebo patients, at 6 months).

Blood pressure fell in both groups during treatment, but was significantly lower in patients allocated candesartan than in those on placebo (p≤0.001 for days 2–7; figure 2). On day 7, mean blood pressure was 147/82 mm Hg (SD 23/14) in the candesartan group and 152/84 mm Hg (SD 22/14) in the placebo group. The mean difference in systolic blood pressure on day 7 was

![Figure 4: Functional status at 6 months’ follow-up](image-url)
5 mm Hg (95% CI 3–7; p=0·0001) and the mean difference in diastolic blood pressure was 2 mm Hg (1–3; p=0·001). During the 6 months’ follow-up, mean blood pressures were similar in the two groups, and at 6 months the mean blood pressure was 143/81 mm Hg in both groups.

Figure 3 shows the analysis of the first co-primary effect variable, the cumulative risk of the composite endpoint of vascular death, stroke, or myocardial infarction. Unadjusted analysis of times to first event showed no significant difference between candesartan and placebo (HR 1·09, 95% CI 0·84–1·41; p=0·53). The result of the key adjusted analysis was very similar (HR 1·09, 95% CI 0·84–1·41; p=0·53). The result of the key adjusted analysis suggested a shift in favour of placebo (OR 1·17, 1·00–1·38; p=0·048). A formal goodness-of-fit test gave no evidence that the proportional odds assumption was violated (p=0·85), and a per-protocol analysis did not affect the result (OR 1·19, 1·02–1·41; p=0·032). As a sensitivity analysis, we undertook a sliding dichotomy analysis using the SSS scores at baseline, which showed unfavourable outcomes for 557 (56%) of 1000 patients on candesartan and 523 (52%) of 1004 patients on placebo (OR 1·16, 95% CI 0·97–1·38, p=0·11; risk ratio [RR] 1·07, 95% CI 0·99–1·16, p=0·11). We also did a conventional fixed dichotomy analysis (mRS 3–6 vs 0–2) and found unfavourable outcomes for 348 (35%) of 1000 patients on candesartan and 331 (33%) of 1004 patients allocated placebo (adjusted OR 1·12, 0·90–1·41, p=0·32; RR 1·06, 0·93–1·19, p=0·39).

Table 3 shows the numbers of the other prespecified clinical events during the 6 months’ follow-up, and figure 3 shows the cumulative risk of all-cause death during follow-up. For all events (death from any cause, vascular death, ischaemic stroke, haemorrhagic stroke, all strokes, myocardial infarction, stroke progression, symptomatic hypotension, renal failure, and symptomatic venous thromboembolism) there were small, non-significant differences in favour of placebo, although the difference was larger for stroke progression (RR 1·47, 95% CI 1·01–2·13; p=0·04). For the secondary clinical outcomes, SSS score at 7 days and Barthel index at 6 months, there were no significant differences between the groups (table 4). The trial did not screen systematically for other adverse events, but for the adverse events reported by the investigators there were no significant differences between the groups (data not shown).

There was no evidence of a differential effect in any of the prespecified subgroups (figure 5). For the subgroup of patients treated very early (<6 h), there was a benefit with candesartan, but only on the composite vascular endpoint, and the interaction was not significant (p=0·08). A post-hoc analysis based on an assumption of a linear trend for the effect of time to treatment yielded an interaction p value of 0·02 for the composite vascular endpoint.

Finally, we did a meta-analysis of all randomised controlled trials of blood-pressure lowering drugs in acute stroke. We selected trials of more than 100 patients and assessed the effect on death or dependency (mRS score ≥3), using a conventional fixed dichotomy approach (figure 6). Overall, there was no evidence of a beneficial effect on functional outcome (RR 1·04, 95% CI 0·97–1·12; p=0·30).

**Discussion**

In this trial, we noted no beneficial effect of blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan in patients with acute stroke and raised blood pressure. For functional outcome, one of the two co-primary effect variables, the distribution of
mRS scores at 6 months was less favourable for patients treated with candesartan than for those on placebo, but the difference was not significant because the p value (0·048) was greater than the threshold of 0·025 required to define significance when two co-primary effect variables are used. For the other co-primary effect variable, the composite vascular endpoint, there was also no significant difference between the treatment groups.

The results for both co-primary effect variables were consistent across the prespecified subgroups. Importantly, the results were similar for all levels of blood pressure, and for both ischaemic and haemorrhagic stroke. Two large trials are further assessing the effect of lowering blood pressure in acute ischaemic (ENOS) and haemorrhagic stroke (ENOS, INTERACT2).37,38

Trials of primary and secondary prevention have shown that angiotensin-receptor blockers prevent stroke more effectively than can be expected from their blood-pressure lowering effects alone.14,16,39 In acute stroke, experimental studies10,11 have also suggested specific neuroprotective effects, and ACCESS11 suggested that candesartan given prematurely on the basis of an interim analysis. The trial result is compatible with the results of previous trials of blood-pressure lowering drugs in acute stroke and high blood pressure. Importantly, candesartan did not affect functional outcome, which was the primary effect variable in ACCESS. ACCESS was a small trial that was stopped prematurely on the basis of an interim analysis. The effect on vascular events could therefore be a false positive finding. Together, ACCESS and SCAST raise doubts over the hypothesis of a specific effect of angiotensin-receptor blockade in acute stroke.

Treatment with candesartan was associated with an increased risk of poor functional outcome compared with placebo with a p value of 0·048, and the directions of the

<table>
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<th>Study</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk ratio IV, random (95% CI)</th>
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<td>Previous trials</td>
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<td>IBEST (1988)</td>
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<td>43</td>
<td>6·0%</td>
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<tr>
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<td>4·5%</td>
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<td>42</td>
<td>4·7%</td>
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<td>31</td>
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<tr>
<td>VENUS (1995)</td>
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<td>4·8%</td>
<td>1·12 (0·82–1·52)</td>
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<td>95</td>
<td>9·3%</td>
<td>0·92 (0·83–1·22)</td>
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| Subtotal (95% CI)      |                  |                |        |                                |
| Total events           | 1422             | 1293           | 81·6%  | 1·04 (0·95–1·14)               |

Test for overall effect: Z=0·92 (p=0·36)

| SCAST                  |                  |                |        |                                |
| Subtotal (95% CI)      |                  |                |        |                                |
| Total events           | 348              | 331            | 18·4%  | 1·06 (0·93–1·19)               |

Test for overall effect: Z=0·87 (p=0·39)

| Total (95% CI)         |                  |                |        |                                |
| Total events           | 3633             | 1624           | 100·0% | 1·04 (0·97–1·12)               |

Test for subgroup differences: χ²=0·97, df=1 (p=0·33), I²=0%

Figure 6: Meta-analysis of trials of blood-pressure lowering drugs in acute stroke: effect on death or dependency (modified Rankin Scale score 3 or more)
shifts were consistent for all levels of disability on the mRS. This finding should not be regarded as statistically significant, because of the more stringent significance level required when two co-primary effect variables are used. However, for all the secondary effect variables there was also a small, non-significant increase in risk for patients treated with candesartan, and the data for the composite vascular endpoint, although the difference between groups is far from statistically significant, also favour placebo. Taken together, these findings might suggest that blood-pressure lowering treatment in acute stroke confers risks. We used a low loading dose of candesartan, but a small effect on blood pressure was seen already on day 2, and a modest blood-pressure reduction was seen from day 4 onwards.

SCAST was a large randomised controlled trial with masked assessments of outcomes, independent and masked adjudication of events, and near complete follow-up, and we believe that the trial has high internal validity. This conclusion is supported by the consistency of the results, in both co-primary effect variables, in all subgroups, and in all the secondary effect variables. Furthermore, we believe that the trial has high external validity and that the results can be generalised to a more general population of stroke patients. The trial was undertaken across many centres in nine countries, the patients included were similar to those admitted to many stroke services, and the screening logs show that patients were excluded for reasons that are common in clinical practice. The trial was closed to accrual earlier than planned and did not reach the original target of 2500 patients, but the decision to stop recruitment was made purely on administrative grounds, without knowledge of the data. As we have discussed, the decision to adopt an ordinal approach to the analysis of functional outcome means that even though recruitment did not reach the target of 2500 patients, the achieved statistical power for this effect variable exceeded its original target.23,24 This gain in statistical efficiency is apparent when one compares the results of the conventional dichotomous analysis with the results of the ordinal regression analysis.

The gain in statistical sensitivity is a major strength of the ordinal regression analysis. This gain needs to be weighed against the unfamiliarity of the method to many readers of clinical trials reports, and the lack of an intuitive interpretation of the common odds ratio.24 Indeed there is a risk of misinterpretation if a reader wrongly interprets the common odds ratio as a risk ratio.24 Another limitation of the analysis is that the assumption has to be met that the underlying odds ratios are the same for each step on the mRS.

In conclusion, we showed no evidence of a beneficial effect of careful blood-pressure lowering treatment with an angiotensin-receptor blocker in patients with acute stroke and raised blood pressure. Instead, for most of the effect variables, treatment with candesartan was associated with a non-significant increased risk. Ongoing trials will help to clarify whether this finding is generalisable or whether there are subgroups of patients or different approaches to blood-pressure management for which a treatment benefit can be obtained. Until these trials have been completed, we see no place for routine blood-pressure lowering treatment in the acute phase of stroke.

**Contributions**
All authors contributed to the interpretation of the data and contributed to the writing of the report. ECS was trial manager, collected and analysed the data, and wrote the first draft of the report. GB, DJ, JK, SL, PSR, ROR, AT, and VT were national coordinating investigators during the trial. PMWB was responsible for the meta-analysis. GDM was trial statistician and responsible for the analysis of data. EB was trial coordinating investigator and coordinated the writing of the report.

**Conflicts of interest**
Some of the authors have previously received payment from pharmaceutical companies, but all of these activities were unrelated to the submitted work. PMWB has received payment for lectures from Boehringer Ingelheim, payment for board membership and expenses related to meetings from Boehringer Ingelheim and Lundbeck, and has accepted support to his institution for academic trials from Boehringer Ingelheim. SL has received payment for lectures from Sanofi-Aventis, Novartis, Solvay MSD, and AstraZeneca. AT has accepted support to his institutions for academic trials from AstraZeneca. VT has received payment for lectures from Abbott and Takeda, payment to his institution for board membership from Shire, Boehringer Ingelheim, Syngis, and MSD Belgium, and expenses related to meetings from Shire and Boehringer Ingelheim. EB has received payment for lectures from AstraZeneca and payment for board membership and expenses related to meetings from Bayer Healthcare. All other authors declare that they have no conflicts of interest.

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**The SCAST Study Group**
E I Nilsen (2006–09), M B Hamre (2007–09); JT consultants
D Perry (2005–10), J Thomassen (2006–10); trial coordinating
E Berge.

Trial steering committee: P M Sandset (chairman), G Andersen,
P M W Bath, E Berge, G Boysen, B Carlberg, P Desfontaines,
B Indredavik, H K Iversen, D Jatzus, S E Kjeldsen, J Kørv,
A Lindgren, S Lidars, G D Murray, P S Richter, R O Rime, D Russell,
E C Sandset, J Schrader, A Tretten, V Thyss, I Thomassen, G Vanhooren,
N G Wåhlgren, T B Wylle; representatives from AstraZeneca
(non-voting): A Fransson, P Hasvold, B Karlson, B Springer.
Event adjudication committee: S Strandgaard (chairman), S Husted,
R Salvesen.

Data monitoring committee: T R Pedersen (chairman), P A G Sandercock,
H Wedel.

Institutions (with numbers of patients and names of principal investigators):
Belgium Cliniques Universitaires Saint Luc (5, A Peeters), CHIC
Clinique de l’Esperance (22, P Desfontaines), AZ Sint Jan
(22, G Vanhooren), AZ Sint Blasius (21, E Van Buggenhout), AZ Kliina
(11, K Merlevede), UZ Leuven (8, V Thyss), Sint Augustinus
(6, W van Landegem), AZ Sint Lucas (2, N Libbrecht),
Virga Jesse ZH Hasselt (1, I Dekkelppe); Denmark Århus
Universitetshospital (33, G Andersen), Bispebjerg Hospital
(23, L I Jespersen), Roskilde Sygehus (14, K Ellemann), Viborg Sygehus
(13, M Z Oksbro), Landsdoksykehuset (12, J Steig, B Steig), Glostrup
Hospital (11, H K Iversen), Fredericia Sygehus (7, U Søsted), Holbæk
Sygehus (5, A M Alj), Søborg Sygehus (5, A M Dorph-Petersen),
Randers Centralsygehus (5, O Davidsen), Holstebro Centralsygehus
(3, K Gesler), Haderslev Sygehus (2, O Rasmussen), Sygehus Vendyssel,
Friederikshavn (2, O Groth), Sygehus Vendyssel, Hjørring
(1, N Svennberg), Frederiksborgs Hospital (1, A Heick); Estonia Tartu
Universität (23, K Jõrgen), West Tallinn Central Hospital (23, K Jõrgen),
Kliniki Sjukhuset (19, H J Johnsen, T Johansen), St Olav’s Hospital,
Avdeling for hjerneslag (19, B Indredavik), St Olav’s Hospital
Ullevål (19, Y Rønning), Akershus universitetssykehus (19, O M Rønning),
Diakonhjemmet sykehus (19, E Sørheim), Akershus universitetssykehus
(18, P M Sandset), Oslo universitetssykehus Rikshospitalet (2, A Dahl),
Vestre Viken Ringerike sykehus(1, J Ilsen), Helse Nordmøre og
Romsdal Molde sjukehus (1, Å H Morsund), Helse Finnmark
Hammerfest sykehus (1, A Akerstedt); Poland Wojewódzki Hospital
(52, G Krychowiak), SPZZOZ Sandomierz (37, P Sobolewski), Szpital
Specjalistyczny Konskie (36, W Bora), Instytut Psychiatry i Neurologii
(35, P S Richter), Akademickie Centrum Kliniczne Akademii
Medycznej w Gliwicach (21, D Gasecki), Mediclinic instant Spital
Specjalistyczny w Warszawie (14, J Zaborski), SPZZOZ w Działdowie
(10, M Zalisz), Szpital Specjalistyczny Jasio (6, S Kosiek); Sweden
Kopings lasarett (104, M Kwiatkowska), Länssjukhuset Ryboh
(63, O Lannemery), Sahlgrenska universitetssjukhuset,
Neurologiklinik (62, J E Karlsson), Alingsås lasarett (62, B Eklund),
Danderyd sjukhus (47, A C Laska), Karolinska universitetssjukhuset,
Neurologiklinik (62, J E Karlsson), Martin Luther Universität
Alfried Krupp Krankenhaus (16, P Berlit), J W Goethe-Universität
(24, M von Mering), Klinikum Bremen Mitte (16, M Ebke, A Schroeter),
Hospital (1, S Tuisku); Klinikum Bremerhaven Reinkenheide
(2, O Groth), Sygehus Vendsyssel, Hjørring
(2, O Schuster), Klinikum (3, K Weissenborn), Heinrich Braun Krankenhaus
(2, S Merkelbach), Klinikum (3, B Griewing), Medizinische Hochschule Hannover
(1, S Tuisku);

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